HIV and Aging - Perhaps Not as Dramatic as We Feared?

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Abstract
Ever since the introduction of highly active antiretroviral therapy (ART) in 1995, HIV infection has been linked to "metabolic" complications (insulin resistance, dyslipidemia, osteoporosis, and others). Studies suggested increased rates of myocardial infarction, renal insufficiency, neurocognitive dysfunction, and fractures in HIV-postitive patients. Even long-term suppression of HIV seemed to be accompanied by an excess of deleterious inflammation that could promote these complications. The aims of this viewpoint paper are to summarize recent data and to examine the possibility that the problem of aging-related morbidity in HIV might not be as dramatic as previously believed.

Tanja Engel and Marieke Raffenberg contributed equally to this work.

Introduction

The dramatic reduction in AIDS-related mortality seen after the introduction of highly active antiretroviral therapy (ART) in 1995 was soon followed by reports suggesting metabolic problems in HIV-positive patients treated with the promising new ART agents. These included insulin resistance, dyslipidemia, osteoporosis, and others. Subsequent studies suggested increased rates of myocardial infarction (MI), renal insufficiency, neurocognitive dysfunction, and bone fractures in HIV-positive patients compared to HIV-negative control persons (Fig. 1).

Each of these conditions has long been known to occur more frequently as individuals get older, hence the more recent notion of "aging-related" complications and the fear that prolonged survival in HIV-positive persons might come at the price of accelerated aging. Potential risk factors included toxicity of ART and other medications, prior immunosuppression, more smokers, and more drug users among HIV-positive persons. Disturbingly, even long-term successful suppression of HIV seemed to be accompanied by an excess of deleterious

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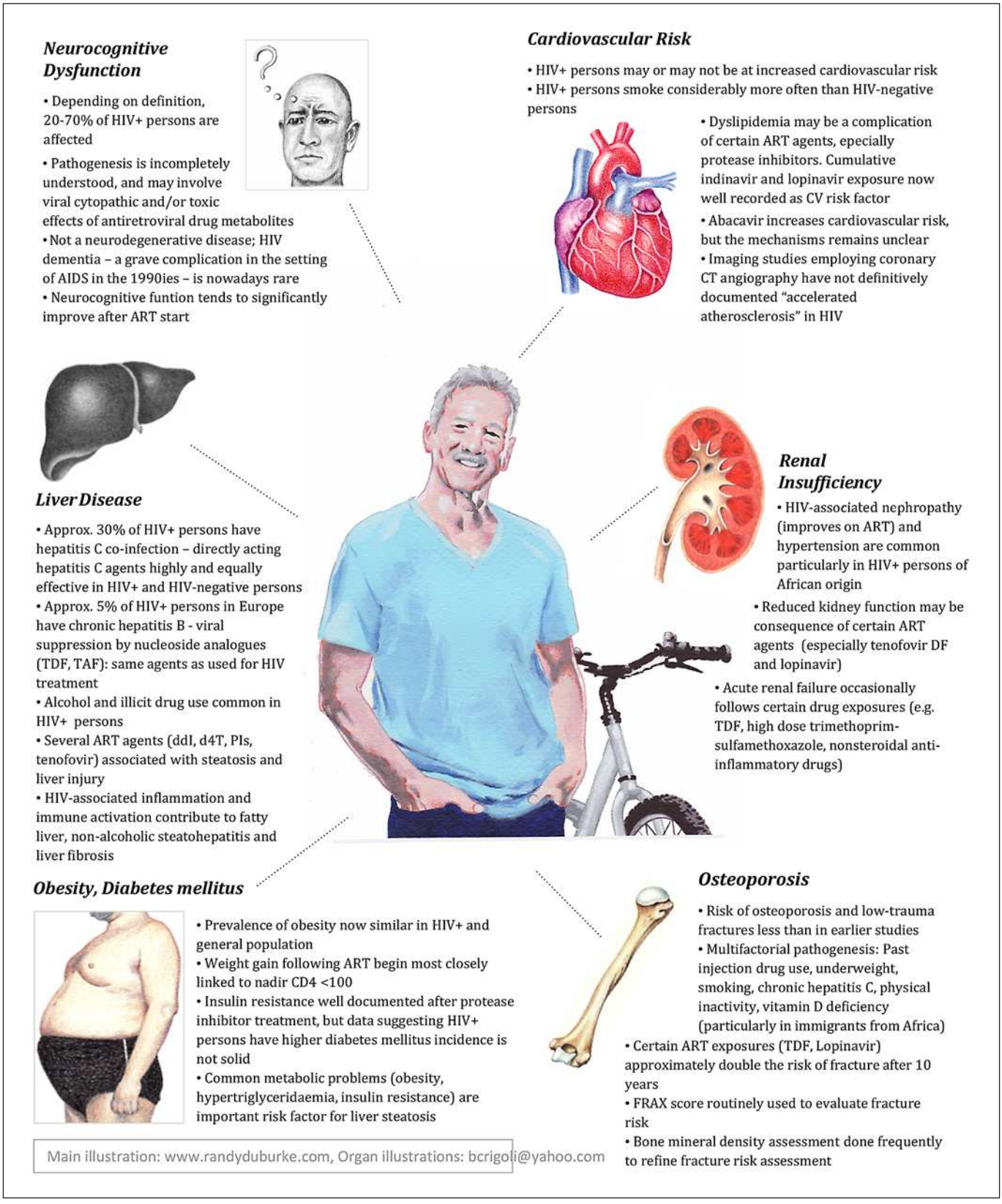

Fig. 1. Major metabolic complications of HIV infection.

inflammation that could promote atherosclerosis, osteoporosis, or neurocognitive decline. The question then was, is HIV invariably followed by premature aging even under the best of circumstances (healthy lifestyle, optimal ART adherence, no smoking or drug use)?

In this viewpoint paper, our aims are to summarize recent data and to examine the possibility that the problem of aging-related morbidity in HIV might not be as dramatic as previously believed.

HIV Infection: More Cardiovascular Events in Initial Reports, Less Dramatic Findings in More Recent Studies

One of the strongest risk factors for cardiovascular (CV) events is advancing age. More than 10 years ago, large studies (>3,000 HIV-positive and >1 million HIV-negative persons) suggested that HIV-positive persons have 2- to almost 4-fold increased CV event rates and more fractures compared to HIV-negative persons, especially when >55 years old [1, 2]. However, no information on smoking or on the prescribed ART agents was available in these studies that came from a single healthcare system in Boston, MA, USA, that were database-derived, and where stringent event validation was not possible. Since then, accelerated atherosclerosis in HIV-positive persons has become a widely held notion, which might be related to procoagulant and proinflammatory mechanisms in the setting of immunosuppression, adverse viral effects on endothelial and other cells, deleterious metabolic effects of certain ART agents, and a high prevalence of smoking and substance use among HIV-positive persons.

Interestingly, a recently updated analysis from the same group in Boston, MA, USA, showed a much smaller difference between HIV-positive and HIV-negative persons with regard to CV events [3]. A widely cited study then estimated an approximately 50% increased CV event rate among HIV-positive compared to HIV-negative US veterans, after adjusting for Framingham risk factors, comorbidities, and substance use [4]. It is uncertain whether these findings can be generalized to non-veterans. A recent large analysis (29,169 HIV-positive persons in the USA and Canada, 335 MIs) applied stringent MI validation, excluded type 2 MIs, and compared event rates with a well-established HIV-negative cohort study. HIV infection was barely significantly associated with a 21% increased CV incidence rate (95% confidence interval, 2–45%), and no significant difference in event rates was seen in those aged >60 years irrespective of HIV infection [5].

Of note, the incidence rate of CV events was the same in 2 recent European cohort studies, when comparing HIV-positive and HIV-negative never-smokers in Denmark [6], and irrespective of smoking status in a HIV cohort study in Switzerland [7]. While these findings require further confirmation, a relevant emerging conclusion is that studies over the past few years suggest smaller differences in CV event rates between HIV-positive and HIV-negative persons than previously recorded, and smoking appears to be a more important CV risk factor than HIV status.

Might Cardiac Imaging Be Useful to Detect Early Subclinical Atherosclerosis?

Given the prevalent notion of an increased CV event rate in HIV-positive persons, considerable interest has been generated by the prospect of early detection of ("subclinical") atherosclerosis before hard CV events have occurred. However, initial studies using carotid intimal medial thickness and coronary artery calcium (CAC) determination have not consistently shown an increased atherosclerosis prevalence in HIV-positive compared to HIV-negative persons [8]. This might be because coronary artery plaque in part is noncalcified in patients aged <50 years, and HIV-positive persons may experience CV events at a young age – perhaps earlier than HIV-negative persons, at least in some studies [9].

Coronary CT angiography (CCTA) can accurately detect noncalcified plaque and predicts CV events better than CAC or carotid intimal medial thickness [10]. In recent large CCTA studies from the USA, inconsistent results were recorded, i.e., an increased [11] and a similar [12] prevalence of noncalcified plaque in HIV-positive compared to HIV-negative persons. An increased duration of ART was associated with subclinical atherosclerosis in these studies [11, 12], but individual ART agents were not associated [13], suggesting that achieving and maintaining virological control may be the more important factors. The lower coronary artery disease rates in central/southern Europe compared to North America highlight the need for European studies. We have recently completed a CCTA/CAC study in Switzerland (428 HIV-positive and 276 HIV-negative participants) [14]. The HIV-positive patients had a similar prevalence of high-risk plaque, but less calcified plaque and lower coronary segment severity and involvement scores. As in the

above-mentioned European studies on CV endpoints [6, 7], traditional CV risk factors contributed to subclinical atherosclerosis but HIV infection did not.

Have Studies on Telomere Length Improved Our Understanding of Aging in HIV?

We think that this is not yet the case. While biomarkers of inflammation and T-cell activation are associated with CV endpoints in HIV, our understanding of the precise mechanisms leading to possibly premature aging in HIV-positive persons remains limited. Leucocyte telomere length (TL) is considered to be a marker of CV aging and increased biological age, and studies on TL are, therefore, of particular interest in the field of HIV. Notably, most data on TL in HIV-positive persons is limited by a cross-sectional design and the absence of appropriate controls; however, it tends to suggest shorter TL in HIV-positive persons compared to HIV-negative controls [15, 16]. Preliminary data on patients with pre- and post-HIV seroconversion measurements suggests that significant TL shortening occurs in the setting of HIV seroconversion [17]. However, there is no solid data suggesting that, after seroconversion, HIV-positive persons have accelerated TL shortening over time compared to HIV-negative persons. Factors such as a longer duration of HIV infection and HIV maximal viral load [15] may be associated with shorter TL and, therefore, – possibly – with aging and atherosclerosis. Large studies in the general population have recorded an association between shorter TL and more atherosclerosis [18], but no such data is yet available in the setting of HIV.

Essentially Normal Life Expectancy with ART in Recent Years

While aging might be accelerated, it is important to note that the mortality of HIV-positive persons has not been increasing in recent years. For example, the annual mortality curve of HIV-positive persons in Switzerland after 1995 is a flat line, with no evidence for any recent increase in the death rate from metabolic complications [19]. In addition, when injecting drug users (who have higher death rates compared to non-users) are excluded from mortality analyses, a consistent finding from numerous cohorts is that persons with well-controlled HIV infection have survival rates that approach those of HIV-negative persons [20]. Indeed, over the past 10 years, the mortality "gap" between HIV-positive and HIV-negative persons in Western countries has considerably narrowed in the setting of effective ART [21].

There are nearly twice as many smokers among HIV-positive men and women in the USA as in the general population, and attempts to quit are made far less frequently and less successfully in the former group [22]. Encouragingly, smoking rates have been decreasing in the past 10 years in HIV-positive persons in Switzerland, even in the subgroup which is most likely to smoke, i.e., injecting drug users [23].

Bone Fractures in HIV – More than Traditional Risk Factors and Choice of ART?

Similar to CV events, a large database-derived study from Boston, MA, USA, identified a 62% increased fracture prevalence in HIV-positive compared to HIV-negative persons without any knowledge of factors with a well-recorded osteoporosis association such as smoking, low BMI, specific ART drugs, or corticosteroid use. A widely cited meta-analysis then estimated that there was a 7-fold increased risk of osteoporosis for HIV-positive persons compared to HIV-negative persons [24] and a considerably increased risk of fractures [2].

In more recent studies, a more moderate increase in fracture incidence has been reported after adjusting for demographics, comorbidities, smoking, alcohol, and BMI. For example, in the Women's Interagency Health Study (WIHS), the fracture risk was 32% increased for HIV-positive versus HIV-negative women [25], and in US veterans, the fracture risk was not increased at all [26]. Similar to CV events, the incidence of trauma fracture appears to be lower in more recent studies and in European populations. For example, the incidence of osteoporotic fracture per 1,000 person-years was reported to be 5.6 in the WIHS, 2.6 in the HIV-positive US veterans, but was only 1.35 in the Swiss HIV cohort (including only validated fractures) [27], and 1.5 in EUROSIDA [28].

Current knowledge suggests that cumulative exposure to tenofovir DF (TDF) and to lopinavir/ritonavir increases the fracture risk [29]. In a large-scale analysis, TDF exposure was associated with an increased risk of osteoporotic fracture of 12% per year, this figure increased to 16% per year when in combination with lopinavir. The recent large EUROSIDA analysis (11,820 persons, 86,118 person-years of follow-up) suggests that not only cumulative TDF exposure may be relevant: patients *ever* exposed to TDF had an almost 2-fold increased fracture risk compared to persons never treated with TDF – and with cu-

mulative TDF exposure, fracture risk did not continue to increase [28]. In contrast, integrase inhibitors, such as raltegravir, are associated with less osteopenia than either TDF [30] or the protease inhibitors atazanavir or darunavir [31]. TAF (tenofovir alafenamide) is a novel version of tenofovir with a more favorable kidney- and bone-toxicity profile. Bone mineral density (BMD) improves when switching to TAF, but – importantly – only when the switch is away from TDF [32].

Renal Insufficiency: Increasingly More Common in the Aging HIV-Positive Population, But Less Nephrotoxic ART Is Now Available

Kidney disease is relatively common in HIV-positive persons [33] and includes conditions associated with untreated HIV infection (e.g., HIV-associated nephropathy), opportunistic infections, systemic immune response to HIV, and ART toxicity [34]. With regard to the effects of antiretroviral agents on the kidney, atazanavir may promote crystalluria and occasionally causes kidney stones, and TDF can cause renal phosphate loss, Fanconi's syndrome, acute tubular necrosis, and ultimately chronic kidney insufficiency. On the other hand, cobicistat, dolutegravir, and trimethoprim may increase the serum creatinine concentration and decrease the *estimated* glomerular filtration rate (eGFR) without, however, affecting the *actual* GFR. Measuring the cystatin clearance may help to overcome this problem. The most accurate method to estimate GFR in HIV may be the Chronic Kidney Disease Epidemiology Collaboration equations [35].

In recent years, the prevalence and incidence rates of kidney disease attributable to aging and metabolic problems (e.g., diabetes, hypertension, atherosclerosis) have increased [36] and may be higher among HIV-positive compared to HIV-negative persons [7, 37]. Therefore, in aging HIV-positive persons, potentially nephrotoxic drugs should be avoided. In particular, less nephrotoxic ART is now available: a change away from TDF to TAF has beneficial effects on GFR, albuminuria, and proteinuria [32].

Body Composition: Old and New Concerns

Lipoatrophy is characterized mainly by decreased limb and facial fat and may be accompanied by increased trunk fat. Lipoatrophy is now recognized as a toxic side effect of past use of thymidine analogue HIV drugs [38]. Unfortunately, lipoatrophy is often not reversible, even after a switch away from thymidine analogues [40]. Importantly, modern ART agents do not appear to cause lipoatrophy [39].

Today, concerns about the body composition in HIV-positive persons have shifted away from lipoatrophy to the problem and complications of obesity and abdominal fat accumulation. Patients commonly perceive their weight gain and obesity as a side effect of ART because the initiation of ART may, in the first 1–2 years, be followed by a significant weight gain. This weight gain correlates by far most closely with a CD4 nadir <100, suggesting that this most likely represents a re-gain of weight which has been previously lost in the setting of progressive immunosuppression [41]. In the 2nd and 3rd year after initiation of ART, the patients' weight appears to stabilize, and there is no evidence in longitudinal studies that HIV-positive persons continue to gain more weight over time than HIV-negative controls [42]. In the past 20 years, however, the median BMI of HIV-positive persons in Switzerland increased significantly (from 22 to 24), in the setting of advancing age, better overall health, earlier start of ART, fewer AIDS events, and a lower percentage of injecting drug users in the HIV-positive population. There is no clear evidence that different ART combinations are associated with more or less weight gain after adjustment for CD4 nadir. It remains to be determined if modern ART regimens are associated with abdominal obesity ("apple shape"), which, even with a normal BMI, has been linked to an increased total and CV mortality rate compared to a fat distribution below the waist ("pear shape") [43].

HIV-Associated Neurocognitive Dysfunction: Poorly Understood but Asymptomatic in Most Cases

Even with successful HIV therapy, early studies showed that 40–70% of all HIV-positive persons are affected by neurocognitive dysfunction. We now know, however, that the vast majority of these patients are asymptomatic; they are referred to as having asymptomatic neurocognitive impairment (ANI) [44, 45]. The ANI concept and the clinical significance of ANI remain debated as, by definition, the asymptomatic impairment of these patients (in at least 2 ability domains) is only uncovered by detailed neurocognitive testing and does not interfere with everyday functioning [46]. *Symptomatic* cognitive impairment has been reported to affect <5% of all HIV-positive persons in recent years, and when present, it is categorized as either mild (mild neurocognitive disorder) or as marked (HIV-associated dementia).

Neurocognitive dysfunction in HIV is currently neither believed to be relentlessly progressive nor is it believed to increase the risk for common neurodegenerative conditions such as Alzheimer disease – however, so far too few HIV-positive persons have reached the age range when Alzheimer risk increases in order to study this question on a large scale. Clearly, HIV-associated dementia has become rare with the introduction of highly active ART.

The initiation of effective modern ART is typically associated with neurocognitive improvement; however, some patients have stable neurocognitive dysfunction and some patients even deteriorate. Additional longitudinal studies are required to better understand the outcome of HIV-associated neurocognitive dysfunction (HAND) in well-controlled patients.

Older age, lower levels of education, immunosuppression, poor ART adherence, ongoing viral replication, and CV risk factors may be associated with HAND [47]. Indeed, additional factors unrelated to HIV that may cause cognitive disorders are quite common in HIV-positive persons (identified in approximately 25% of all HIV-positive patients in a recent Swiss study) [48] and need to be excluded prior to concluding that the patient suffers from HAND. These include psychiatric disorders such as depression, prior central nervous system (CNS) opportunistic infections, CNS trauma, and illicit drug use.

International HIV guidelines recommend screening for HAND, and some groups practice screening at regular intervals. When neurocognitive impairment is identified, neurological referral for brain imaging and cerebrospinal fluid examination is recommended.

The pathogenesis of HAND remains incompletely understood and may include ongoing viral replication in the CNS, despite HIV control in the peripheral blood, due to suboptimal penetration of certain ART agents [49]. Alternatively, ART agents may penetrate well into the CNS, and ART or certain ART metabolites might cause direct neurotoxicity. It remains debated whether CNS "penetration scores" of individual ART agents are useful for routine clinical HIV care.

HIV: More Comorbidities and More Frailty, but Frailty Assessment Is Controversial in Relatively Young HIV-Positive Populations

Numerous factors may contribute to possibly premature aging in HIV, including ART toxicity, coinfections with hepatitis B and C, higher rates of smoking, alcohol, and drug use, and residual inflammation despite suppressive ART. Aging-associated conditions are, however, easier to study than the aging process per se. One important notion that has emerged is that comorbidities might not occur prematurely in HIV-positive persons but perhaps at an increased rate; hence, "accentuated" might be the more appropriate term than "accelerated" aging in HIV-positive persons [50]. Along these lines, HIV-positive persons also seem to take more comedications than the general population [36, 51].

An important concept in geriatric medicine that has only in recent years been applied in the field of HIV is frailty. This is variably defined as a syndrome of decreased physiological reserve and resistance to stressors and is said to be associated with increased morbidity and mortality in the general elderly population [52]. The frailty phenotype was defined by unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. A number of studies now show that HIV infection might be independently associated with frailty in middle-aged HIV-positive patients compared with HIV-negative controls [52, 53]. Drug use, lower educational level, abnormal fat distribution, smoking, physical inactivity, increased levels of inflammatory biomarkers, and hepatitis C coinfection may contribute to frailty [52]. However, there are inconsistencies between studies (e.g., with regard to risk factors and any association with certain antiretroviral agents) that have limited the generalizability of these results.

Gait speed and grip strength have been recorded to predict functional decline and death in elderly populations. In the multicenter AIDS cohort study [54], average grip strength was normal, and there was no difference between HIV-positive and HIV-negative men aged >50 years. However, HIV-positive men had a more rapid decline in grip strength and clinical weakness occurred earlier. Factors contributing to frailty in HIV may include older age, lower BMI, diabetes mellitus, chronic kidney disease, peripheral neuropathy, and higher cumulative HIV viral load correlated with a greater longitudinal decline in grip strength [54].

Frailty is increasingly recognized as an important HIV-associated non-AIDS condition, but frailty assessment is usually not done in routine HIV care – in Swiss HIV outpatient clinics, there is limited time, space, and personnel for this. Moreover, concern has been expressed that the frailty concept was developed in geriatric populations, i.e., it is unclear if this concept is clinically useful in HIV-positive populations whose median age in Western countries remains <50 years.

Table 1. Selected drug-drug interactions in aging HIV-positive persons

Drug classes	Antiretrovirals	Comments
Antacids H_2-receptor blockers Proton pump inhibitors	Atazanavir Rilpivirine	• Atazanavir/rilpivirine solubility decreases as pH increases • Antacids, H_2-receptor blockers: separate drug intake • Proton pump inhibitors: not recommended
Antacids Divalent cations (iron, calcium, magnesium)	Dolutegravir Elvitegravir/c Raltegravir	• Integrase inhibitors form a complex with divalent cations at the level of the gastrointestinal tract which reduces their absorption • *Dolutegravir*: administer 2 h before or 6 h after antacids or mineral supplements • *Elvitegravir/c*: separate from antacids or mineral supplements by at least 4 h • *Raltegravir*: not recommended with aluminum or magnesium antacids. Coadministration with calcium carbonate antacids is possible when raltegravir is administered twice daily (400 mg b.i.d.) but is not recommended for once daily administration of raltegravir (1,200 mg q.d.). Separate administration by at least 4 h with mineral supplements
Corticosteroids*	Boosted PI Elvitegravir/c	• Inhibition of steroid metabolism can increase the risk of Cushing syndrome and adrenal suppression. Risk is not limited to oral administration but has been documented with topical, ocular, intra-articular, intrathecal administration of steroids • *Budenoside, fluticasone, triamcinolone, mometasone* are contraindicated
Antidepressants*	Boosted PI Elvitegravir/c	• In general, tricyclic antidepressants should be avoided in older patients due to peripheral (constipation, orthostatic hypotension) and central anticholinergic side effects (sedation, confusion, delirium). Side effects can be exacerbated by inhibition of their metabolism
Benzodiazepines*	Boosted PI Elvitegravir/c	• Benzodiazepines should be generally avoided in the elderly owing to the increased sensitivity to benzodiazepines and increased risk of cognitive impairment, delirium, falls and fractures. These effects can be exacerbated by inhibition of their metabolism. Use at the lowest dose and for a short duration • *Midazolam, triazolam*: contraindicated
Vitamin K antagonists*	Boosted PI Elvitegravir/c	• Vitamin K antagonists are metabolized by cytochromes. DDIs with boosted regimens are managed by adjusting the dose according to INR • Dose adjustments might be needed when switching pharmacokinetic booster, since ritonavir has inducing properties on cytochromes whereas cobicistat does not
Direct acting anticoagulants*	Boosted PI Elvitegravir/c	• Substrates of cytochromes and/or transporters and therefore are subject to significant DDIs • Their effect cannot be measured routinely and there are limited data on the management of DDIs; therefore, the use of direct acting anticoagulants should be avoided with boosted regimens
Antiplatelet agents	Boosted PI Elvitegravir/c Efavirenz Etravirine Nevirapine	• *Clopidogrel*: converted to active metabolite via cytochromes. Boosted regimens and etravirine are likely to reduce activation thereby leading to non-responsiveness to clopidogrel. Alternatives to clopidogrel should be considered. Note: efavirenz and nevirapine may increase activation and therefore should be used with caution • *Prasugrel*: converted to active metabolite via cytochromes. Coadministration of strong inhibitors or inducers of cytochromes was shown to have a limited effect on prasugrel antiplatelet effect. Coadministration is possible with boosted regimens, efavirenz, etravirine and nevirapine • *Ticagrelor*: contraindicated with boosted regimens as may substantially increase ticagrelor concentrations and the risk of bleeding
Calcium channel inhibitors*	Boosted PI Elvitegravir/c	• Inhibition of metabolism is expected to increase calcium channel inhibitors concentrations and thereby the hypotensive effect • Start at a lower dose and titrate based on response to therapy • *Amlodipine*: a dose reduction of 50% may be considered
Statins*	Boosted PI Elvitegravir/c	• Can significantly increase the exposure of some statins and thereby increase the risk of rhabdomyolysis • *Simvastatin, lovastatin*: contraindicated • *Other statins*: start with low dose and titrate to effect • *Pitavastatin*: use of standard dose is possible

Table 1 (continued)

Drug classes	Antiretrovirals	Comments
Antidiabetics*	Boosted PI Elvitegravir/c Dolutegravir	• *Sulfonylureas*: potential increase in concentrations by boosted regimens, monitor effect and reduce sulfonylureas dose if needed • *Metformin*: dolutegravir increases metformin exposure due to inhibition of the renal transporter OCT2. Dose adjustment of metformin should be considered when starting dolutegravir • *Saxagliptin*: dose should be limited to 2.5 mg daily with boosted regimens • *Exenatide, linagliptin, liraglutide, sitagliptin, vildagliptin*: no DDIs with boosted regimens
Erectile dysfunction agents*	Boosted PI Elvitegravir/c	• *Sildenafil*: do not exceed 25 mg in 48 h • *Tadalafil*: do not exceed 10 mg in 72 h • *Vardenafil*: do not exceed 2.5 mg in 72 h
Cancer drugs*	Boosted PI Elvitegravir/c	• Multiple cancer drugs are metabolized by cytochromes and therefore are subject to significant DDIs leading to cancer drug-related toxicities. Limited data to guide DDI management. Antiretroviral drugs with a low potential for metabolic DDIs (raltegravir, dolutegravir) should be favored when possible
Non-steroidal anti-inflammatory drugs	TDF	• Coadministration may increase the risk of nephrotoxicity. Avoid long-term use and closely monitor renal function

For more detailed information, visit www.hiv-druginteractions.org, or refer to [64, 65].

"Boosted" refers to boosting with either ritonavir or cobicistat.

c, cobicistat; DDI, drug-drug interactions; INR, international normalized ratio; PI, protease inhibitors; TDF, tenofovir disoproxil fumarate.

* Non-nucleoside reverse transcriptase inhibitors such as efavirenz, etravirine, and nevirapine are predicted to lower the concentrations of some comedications. Dose adjustment of the comedication might be needed.

Aging: Higher Risk for Drug-Drug Interactions, More Therapeutic Challenges

With aging of the HIV-positive population, medication-related problems are emerging as an important challenge, including polypharmacy and a higher risk for drug-drug interactions (DDIs) [55]. Several antiretroviral drugs can interact with comedications used for the treatment of comorbidities in the aging population due to their inhibitory properties and/or they induce effects on drug-metabolizing enzymes and/or drug transporters which can lead to drug toxicity or loss of efficacy of the coadministered drug. On the other hand, comedications frequently used in elderly individuals (e.g., gastric acid-reducing agents or mineral supplements) can interfere with the absorption of certain antiretroviral drugs and thereby compromise their efficacy. Selected DDIs in the aging HIV-positive population are shown in Table 1. More information can be found in the University of Liverpool's HIV DDI database (www.hiv-druginteractions.org).

Aging of the HIV population is also complicated by traditional medication-related problems observed in geriatric medicine. For example, the prescription of corticosteroids can complicate blood glucose control in patients with diabetes. Additional issues regard drug-disease interactions in the presence of multiple comorbidities [56], the decline in the function of organs (which may impact pharmacokinetics and thus drug dosing), and aging can impact drug pharmacodynamics [56] (e.g., elderly individuals can be more sensitive to the effect of drugs such as benzodiazepines) [57].

Altogether, the presence of comorbidities and age-related physiological changes predispose elderly HIV-infected individuals not only to a higher risk for DDI, but also to the use of inappropriate drugs [58]. Thus, all prescriptions should be carefully reviewed. Finally, it may be worth exploring our patients' perceptions of their ART and their comedications in detail: in a recent Swiss study, patients attributed more priority to their ART than to their comedications, and self-reported adherence to comedications was worse [59].

What Should We Do about Metabolic Complications in HIV?

Most importantly, the same health recommendations as for the general population also apply to patients living with HIV: healthy nutrition, physical activity, smoking cessation, as well as treatment of hypertension and dyslipidemia. International guidelines now recommend screening for the most important comorbidities. To prevent the loss of BMD and to lower the risk of fractures during ART, it is reasonable to start concomitant vitamin D_3 (and calcium supplements, if dietary calcium intake is inadequate), because BMD loss tends to be most pronounced in the first year following ART initiation, in particular with TDF, and tends to plateau after that [60].

Some HIV experts would recommend avoiding protease inhibitors altogether, given that they compare unfavorably with non-nucleoside reverse transcriptase inhibitors or integrase inhibitors with regard to multiple metabolic endpoints. Similarly, many HIV experts would avoid abacavir, given the association of abacavir with CV endpoints in some but not all studies. From a bone and renal health standpoint, it is probably reasonable to avoid TDF and use only TAF – however, some experts contend that the renal and BMD benefits to be expected from TAF [32] are not large enough to justify switching from TDF (now available as generic medication in many countries) to the more expensive TAF.

Finally, some HIV clinicians actively stop the "third agent" (TDF, ABC) for reasons of bone, renal, and CV health, arguing that evidence from randomized trial for the virological efficacy of dual therapy – using, e.g., 3TC and a protease inhibitor – is now solid [61, 62]. Those who avoid protease inhibitors are now using 3TC or FTC in combination with dolutegravir with success (dolutegravir monotherapy is not recommended today because the virological failure rate is too high), and virological failure with such dual therapy has been rare [63]. The manufacturer of dolutegravir is actively pursuing the dual therapy strategy by sponsoring large randomized studies of 3TC in combination with dolutegravir.

Conclusion

There is no doubt that we are seeing more elderly HIV-positive persons, and more of them have aging-related issues such as CV events, osteoporotic fractures, obesity, neurocognitive disorders, renal insufficiency, frailty, and DDIs than 20 years ago. However, the life expectancy of HIV-positive and HIV-negative persons is now essentially the same – this applies to most patients today who are not injecting drug users, non-smokers, and are treated with modern ART regimens. Adjustment for all relevant risk factors remains crucial in epidemiological studies of aging-related complications in HIV. We await with interest further studies looking into the notion of accelerated aging in HIV – could this have been a premature conclusion and a problem perhaps not quite as bad as we feared?

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